Update
Le point

Articles in the **Update** *series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.*

Les articles de la rubrique **Le point** *fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.*

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Japanese encephalitis: current worldwide status*

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The changing epidemiological and distribution patterns of Japanese encephalitis in various southern and east Asian countries are described. Immunization is considered to be the only practical way to control the infection. Several vaccines have been developed and two types of inactivated vaccine are now available for use in man.

Japanese encephalitis (JE) is a serious public health problem with significant mortality in children and old people in many countries of Asia. It is one of the main concerns of the WHO Regional Offices for South-East Asia and the Western Pacific, the World Health Organization having for many years assumed a coordinating role in this field.

EPIDEMIOLOGY

In recent years the epidemiological patterns and especially the distribution of Japanese encephalitis have changed. The disease incidence appears to be subsiding in China, Japan, and the Republic of Korea, but at the same time has been increasing and spreading over parts of Bangladesh, Burma, India, Nepal, Thailand, and Viet Nam. The reasons for these changes are not clear but the following factors may be involved:

(1) changes in agriculture such as adoption of paddy (rice) cultivation, use of pesticides, and establishment of large modern pig farms;
(2) changes in socioeconomic status involving a shift to rice cultivation from dry land crops and the promotion of pig breeding as a food source;
(3) climate, including effects of temperature and rainfall;
(4) effects of vaccination of the human population and pigs, the amplifying host;
(5) possible role of additional potential amplifying hosts other than pigs; and
(6) the wide variety of mosquito species in south-east Asia, and their different vectorial capacities.

* A French translation of this article will appear in a later issue of the *Bulletin*.

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Table 1. Two epidemiological patterns of Japanese encephalitis

Climatic zone	Occurrence of disease	Country, region	Season
Tropical	Endemic, with sporadic cases	South India, Indonesia, Malaysia, Singapore, south Thailand	No seasonal pattern
Northern part of tropical zone	Outbreaks	China, Japan, Republic of Korea, and Nepal; northern parts of Burma, India, Thailand, and Viet Nam	Late summer and autumn (end of rainy season)

Of special interest are certain contrasting areas such as north Thailand where Japanese encephalitis is common and south Thailand where it is rarely encountered, although the vectors, the amplifying hosts, and the virus are apparently abundant in both areas. This seeming paradox is unexplained.

Epidemiologically, two characteristic patterns appear to be related to climatic and seasonal conditions. As can be seen in Table 1, in the tropical zone the disease occurs as sporadic cases throughout the year with no seasonal pattern. This type of epidemiological pattern is characteristic of southern India, Indonesia, Malaysia, Singapore and southern Thailand. However, in the northern part of the tropical zone outbreaks occur occasionally, reaching epidemic proportions at the end of the rainy season when mosquito populations are maximal. These outbreaks have taken place in China, Japan, the Republic of Korea, Nepal, and the northern parts of Burma, India, Thailand and Viet Nam. An outbreak may be of short duration (2–3 months); in West Bengal and Tamil Nadu (India), however, cases of encephalitis have continued for a period of 4–6 months.

Table 2 presents some epidemiological characteristics of Japanese encephalitis by country.

Burma. The first outbreak was noted in 1974 and cases have been reported every year until 1980 in Shan State. In 1977 Japanese encephalitis was reported for the first time outside this state; 5–43 cases are reported in the country every year, with a case-fatality rate of 15–21%. No cases have been reported since 1980.

China. Japanese encephalitis is prevalent in all provinces, except Xinjiang (Sinkiang), Shanghai, and Xizang (Tibet). Over 10 000 cases are reported annually with a case-fatality rate of about 10%. In the past decade the infection moved into a new epidemic area north of 45° N latitude in Inner Mongolia. In 1974 the disease became epidemic in a human population that previously had no JE antibody.

India. Japanese encephalitis has been focally endemic for decades in the southern India States of Karnataka and Andhra Pradesh. Prior to 1970, cases were recorded only from these States. In 1973, a large outbreak occurred in West Bengal. The end of 1977 and the year 1978 were characterized by the occurrence of extensive outbreaks in north-eastern India with 7463 cases reported. In the north, Uttar Pradesh experienced its first epidemic in 1979 and the disease has continued there with 1716–3894 cases per year. In 1982, the disease occurred for the first time in the western coastal region (in Goa).

Japan. Since 1967, Japanese encephalitis has been an uncommon disease with an average of fewer than 100 cases per year. It has become a disease of the older age groups, the case-fatality rates being higher in the elderly. A gradual decrease of herd immunity in older persons has been taking place, creating a potential for future disease outbreaks.

Republic of Korea. Prior to 1969 Japanese encephalitis occurred annually in the Republic of Korea, with over 1000 cases per year and case-fatality rates of over 40%. During the 1970s the numbers decreased to an average of 86 cases per year, with case-

Table 2. Japanese encephalitis in various countries

Country	Geographical distribution and year	No. of cases annually	Case-fatality rate (%)	High-risk groups
Burma	Shan State since 1974; other areas since 1977; no cases since 1980	5–43	15–21	All age groups
China	All provinces (except Xinjiang, Shanghai, and Tibet)	> 10 000	10	Children under 15 years
India	South India only (before 1970)	100 (average)	21–40	Children under 15 years
	North and north-east: 1978	7463		All age groups
	1979–83	1716–3894		
Japan	Western prefectures: before 1967	> 1000	30	Shift to older age groups
	after 1967	100 (average)		
Republic of Korea	All provinces (prevalent in southwestern part before 1969)	> 1000	> 40	
	During the 1970s	86 (average)	5.8	Children under 15 years; modest shift to young adults
	1982	1179	3.3	
	1983	139	10.8	
Nepal	First outbreak in 1978 in the south; 10 out of 14 administrative zones	55–843	35.4	All age groups
Thailand	North and north-east: 1970	986	20–30	Children under 15 years
	1971–79	1600		
	1980	2143		
	1981	2432		
	South Thailand	Sporadic cases		
Sri Lanka	All provinces	Sporadic cases		Children under 15 years
Indonesia, Malaysia, Singapore		Sporadic cases		

fatality rates about a tenth of previous figures. In 1982, in spite of an estimated 80% vaccination coverage among schoolchildren, an unexpected epidemic struck the rice-growing areas in the south-west with 1179 serologically confirmed cases and a case-fatality rate of 3.3%. Some of these cases were in vaccinated children, although a modest shift in the age of cases from children to young adults suggests that without vaccination the disease in children might have been more prevalent.

Nepal. Outbreaks of Japanese encephalitis were first recognized in 1978 to be of public health importance. Since then from 55 to 843 cases have been reported every year, affecting all age groups.

Sri Lanka. JE virus was first isolated in 1968 and, since then, cases have been reported every year from pigs and large rice-growing areas. Acute encephalitis accounts for over 1000 hospital admissions each year, but only 30 cases in the last 10 years were confirmed serologically.

Thailand. The first outbreak of Japanese encephalitis was reported in Thailand in 1969, since when it has become an increasingly reported disease. Outbreaks have been reported every year mainly in the north and northeastern regions, with considerably high morbidity rates (see Table 2). Recently the disease seems to be spreading in the south.

Indonesia, Malaysia, Singapore. Low priority is given to Japanese encephalitis among

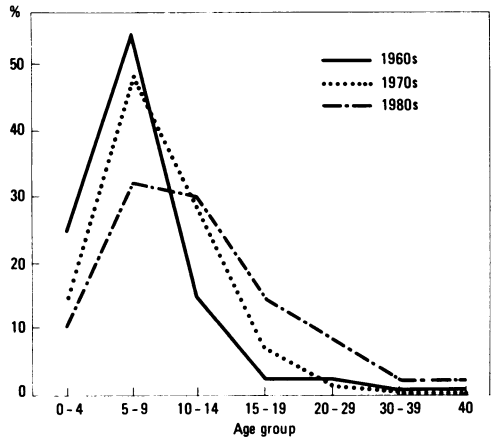

Fig. 1. Age distribution of Japanese encephalitis cases in the Republic of Korea from the 1960s to 1980s.

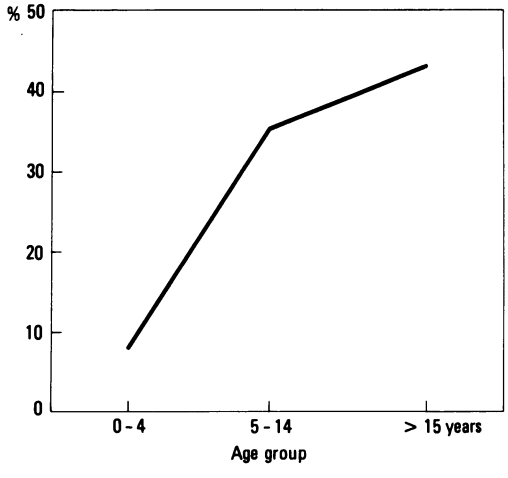

Fig. 2. Age distribution of Japanese encephalitis cases in Nepal.

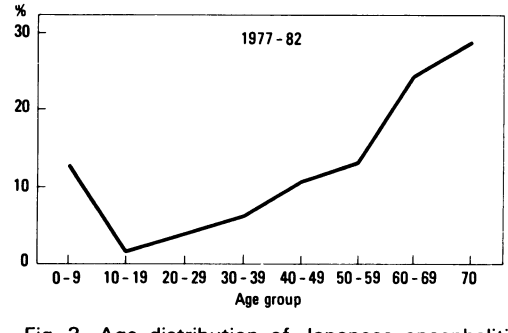

Fig. 3. Age distribution of Japanese encephalitis cases in Japan, 1977–82.

public health problems in these countries because the disease occurs only sporadically, although the environmental conditions appear to be favourable for JE outbreaks.

Age and sex incidence

Children bear the major brunt of the disease in all the regions. There are, however, differences in the age incidence in different areas. The disease affected mainly the 2–5-year age group in China (Province of Taiwan), and schoolchildren in the Republic of Korea (Fig. 1) and southern India. In the northern and northeastern parts of India and Nepal (Fig. 2), both children and adults of all age groups were affected. This suggests that the virus in these areas was recently introduced into a relatively non-immune population. In Japan many cases were recorded among elderly people since children are vaccinated at school (Fig. 3); in most of the epidemics, the incidence in males was higher than in females.

Role of animals

Although pigs are considered to be "amplifiers" of JE virus transmission in many countries, some like India have a much lower ratio of pigs to humans than other Asian countries with pork-eating populations. In India, however, cattle and buffalo are numerous (compared to pigs) but there is no evidence that they are natural hosts of the virus. Therefore, determination of the exact role of domestic animals in the transmission of JE virus and disease in Asian countries is now considered to be an important subject for research.

PREVENTION AND CONTROL ACTIVITIES

Animal vaccines

Live attenuated JE vaccine has been developed in Japan primarily for immunization of pigs to prevent still births (Table 3). In China, live vaccine prepared in

Table 3. Present status of JE vaccine production and vaccination in five countries

Country	Killed vaccine			Live vaccine
	Substrate	No. of annual doses	Target population	
China	Primary hamster kidney-cell culture	About 70 million	Children under 10 years	Pilot project in humans
India	Mouse brain	2 million (by 1986)	To be determined	–
Japan	Mouse brain[a]	10–12 million	Children 3–15 years	Vaccination of pigs to prevent still births
Republic of Korea	Mouse	4–6.5 million	Children 3–15 years	Vaccination of pigs (BHK cells)[b]
Viet Nam	Mouse brain	Small scale	Children 3–15 years	–

[a] Recently the bivalent vaccine has been used.
[b] BHK: baby hamster kidney cell culture.

primary baby hamster kidney cell culture has been used for vaccination of horses. In the Republic of Korea live attenuated JE vaccine using baby hamster kidney cells has also been developed and used for the vaccination of pigs.

Immunization of pigs may be attempted to control JE epidemics because it has been established that these animals, after vaccination with the live vaccine, showed no viraemia on exposure to infected mosquitos. The immunized pigs must have therefore been unable to "amplify" the virus transmission. However, all investigators engaged in this project pointed out that effective immunization was not easy because of the high turnover in the pig population so that individual pigs might escape being immunized.

Human vaccines

(*a*) *Inactivated vaccines.* At present two types of inactivated vaccine are in use, one derived from mouse brain and the other from primary baby hamster kidney cells. The mouse brain vaccine is highly purified, well-defined and has been adapted for production in several countries (Table 3). JE virus strains appear to be clustered into two antigenic groups. The inclusion of one strain from each antigenic group (Nakayama and Beijing) in the vaccine has improved its potency. In China, killed monovalent JE vaccine has been produced using baby hamster kidney cell culture; approximately 70 million children are immunized with this vaccine every year. The published data in China on killed vaccine indicates that the vaccine is efficacious and safe when applied to people. In Japan and the Republic of Korea, killed monovalent JE vaccine prepared from infected mouse brain tissue has been produced and used for large-scale vaccination of people. Bivalent killed JE vaccine has also been developed in Japan. In Viet Nam, killed JE vaccine prepared from infected mouse brain tissue has been produced on a small scale.

The Government of India decided in 1982 that freeze-dried mouse brain vaccine should be produced with Japanese collaboration during the period 1982–86, so that 2 million doses of vaccine will be available by 1986. Selection of the target human population for this vaccination will be done after completion of morbidity studies. The development of a JE vaccination strategy in India needs careful consideration before it can be implemented.

(*b*) *Live vaccines.* In China, an experimental live attenuated JE vaccine using primary baby hamster kidney cell culture has been developed and has undergone extensive field

trials in people. Further studies to characterize candidate strains are needed.

Immunization provides a reasonable and practical way to control Japanese encephalitis, but the selection of target populations may present a problem in countries where JE outbreaks cannot be clearly defined in terms of places of infection and affected age groups. However, immunization is recommended for protecting populations where JE virus attacks are highly probable. Monitoring of JE activity will help to identify populations at risk of exposure who can then be given a booster immunization.

It should be mentioned that JE vaccine is not always available because the cost of commercial vaccines is still too high for use in large-scale vaccination. Work on the development of second generation (genetically engineered) vaccines is in progress.

Monitoring and control of vector and amplifier of JE virus

Monitoring the spread of JE virus in pigs by measuring the antibody titre by haemagglutination inhibition has been conducted in Japan and the Republic of Korea. As already mentioned, in both countries pigs have been immunized with killed vaccine or live attenuated vaccine.

In China, Japan, the Republic of Korea, and Viet Nam, monitoring of outbreaks and control of vector mosquitos have been regularly conducted. However, since *Culex tritaeniorhyncus,* an important vector mosquito of JE virus in Asia, emerges mainly from the irrigation water of rice paddy fields covering vast areas, the application of insecticides to these areas for vector control purposes is not practical. One of the main problems is therefore the integration of JE vector control measures at the national level with existing measures to control other infectious diseases, together with the primary health care approach.

WHO activities and research

WHO has periodically convened groups of experts in order to review and discuss progress in epidemiological studies and in prevention and control of Japanese encephalitis. During the period 1979–84 WHO convened the following:

(*a*) an interregional meeting on Japanese encephalitis on 19–24 March 1979 in New Delhi, where technical guidelines were formulated;

(*b*) a joint consultative meeting on arthropod- and rodent-borne viral rickettsial diseases from 31 May to 3 June 1982 in Bangkok, which reviewed surveillance, prevention and control programmes of Japanese encephalitis and outlined a plan of action to meet identified problems;

(*c*) a working group on the prevention and control of Japanese encephalitis on 19–21 December 1983 in Tokyo, which also reviewed and discussed the production of killed monovalent and bivalent JE vaccines and diagnostic reagents;

(*d*) a working group on development of vaccines for arthropod- and rodent-borne viruses on 29–31 August 1984 in Sendai, Japan, which reviewed progress in the development of bivalent and live attenuated JE vaccines and in the research on subunit JE vaccine.

The Organization's efforts in the future will be directed towards collaboration in the following activities:

(1) identification of the impact of Japanese encephalitis and strengthening of surveillance systems;

(2) studies of the factors involved in the recent increase of JE outbreaks in areas where the virus has been silently in circulation for the past 10–20 years (e.g., in parts of India, Nepal);

(3) studies on mosquito vector ecology as well as the role of natural hosts of JE virus besides pigs and birds;

(4) development of a cheap and effective vaccine;

(5) development of rapid diagnostic methods and production of reagents;

(6) definition of national strategies for prevention and control; and

(7) comparison of potency tests and standardization of vaccines using the most appropriate methods, for which high priority is needed.